

UNITED STATES SPECIFICATION

TO ALL WHOM IT MAY CONCERN:

BE IT KNOWN THAT WE, **ALFRED POPP**, a German citizen, residing at Bürgermeister-Prenn-Strasse 8, D-82008 Unterhaching, Germany; **JÜRGEN STOHRER**, a German citizen, residing at Michl-Lang-Web 9, D-82049 Pullach, Germany; **HERMANN PETERSEN**, a German citizen, residing at Karl-Gros-Strasse 11, D-84489 Burghausen, Germany; **ANDREA GILCH**, a German citizen, residing at Bergstrasse 11b, D-85419 Mauern, Germany; and **JODOCA ROCKINGER-MECHLEM**, a German citizen, residing at Meginhardstrasse 52, D-82205 Gilching, Germany have invented certain new and useful improvements in a

A PROCESS FOR THE ENZYMATIC PREPARATION OF ENANTIOPURE 1,3-DIOXOLAN-4-ONE AND 1,3-OXATHIOLAN-5-ONE DERIVATIVES

of which the following is a specification.

BACKGROUND OF THE INVENTION

1. Field of the Invention

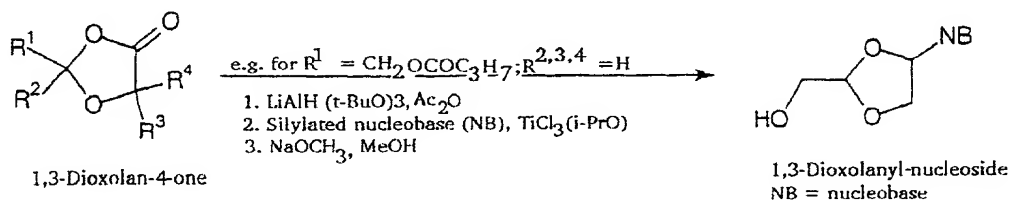
The invention relates to a process for the enzymatic preparation of enantiopure 1,3-dioxolan-4-one and 1,3-oxathiolan-5-one derivatives.

2. The Prior Art

Enantiopure derivatives are used as starting materials and intermediates in the synthesis of agrochemicals and pharmaceuticals. Many of these compounds are currently prepared and marketed as racemate or mixture of diastereomers. However, in many cases, the desired physiological effect is brought about by only one enantiomer/diastereomer. The other isomer is, in the most favorable case, inactive, but it may also counteract the desired effect or even be toxic. Processes for separating racemates are therefore of increasing importance for the preparation of compounds of high enantiopurity.

It is known that racemates of chiral compounds can be separated with the aid of enzymes. A large number of

publications describe enzymatic kinetic resolutions of racemates of esters with lipases and esterases. However, to date, there is no process which permits the simple separation of 1,3-dioxolan-4-one and 1,3-oxathiolan-5-one derivatives. Enantiopure 1,3-dioxolan-4-ones are of great interest for the preparation of compounds with antiviral activity, such as, for example, the 1,3-dioxolanyl-nucleoside "dioxolane-T" (NB = thymine in equation 1) and similar structures (*Bioorg. Med. Chem. Lett.* 1993, 3(2), pp. 169-174).

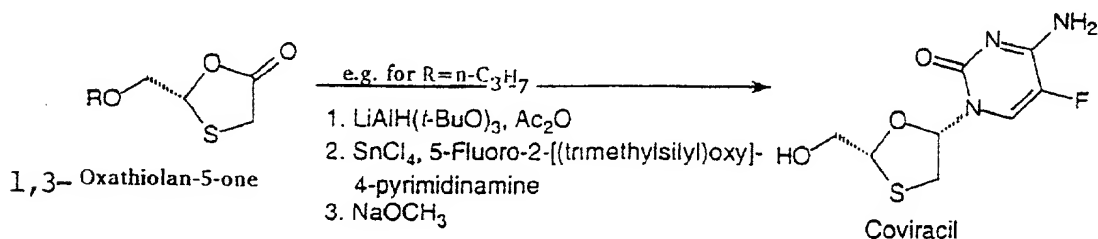


Equation 1

For preparing enantiopure 1,3-dioxolanyl-nucleosides, the separation into the enantiomers has to date been carried out at the considerably more costly nucleoside stage. This process was described for the first time by L.J. Wilson et al. (*Bioorg. Med. Chem. Lett.* 1993, 3(2), pp. 169-174). The butyric ester of the primary hydroxyl group of a 1,3-dioxolanyl-nucleoside is in this case hydrolyzed with the aid of pig liver esterase, and the two pure enantiomers are thus

obtained in good optical yields. WO 00/22157 (inventors: Yao, Y. et al.) describes a variant of this process by resolution in nonhomogeneous systems.

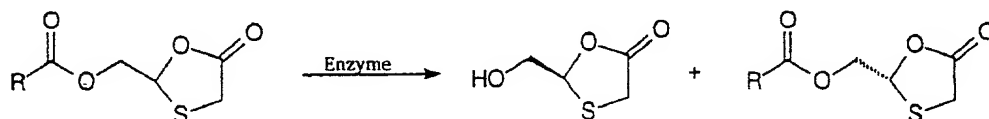
Enantiopure 1,3-oxathiolan-5-ones are likewise of great interest for the preparation of compounds with antiviral activity, such as, for example, the 1,3-oxathiolanyl-nucleoside Coviracil® (also Emtricitabine, formerly FTC, 4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone; equation 2) and similar structures (*J. Org. Chem.* 1992, 57(21), pp. 5563-5565, WO 91/11186, WO 92/14743, WO 00/22157).



Equation 2

For preparing enantiopure 1,3-oxathiolanyl-nucleosides it is possible for the separation into the enantiomers to take place at various stages. Thus, an

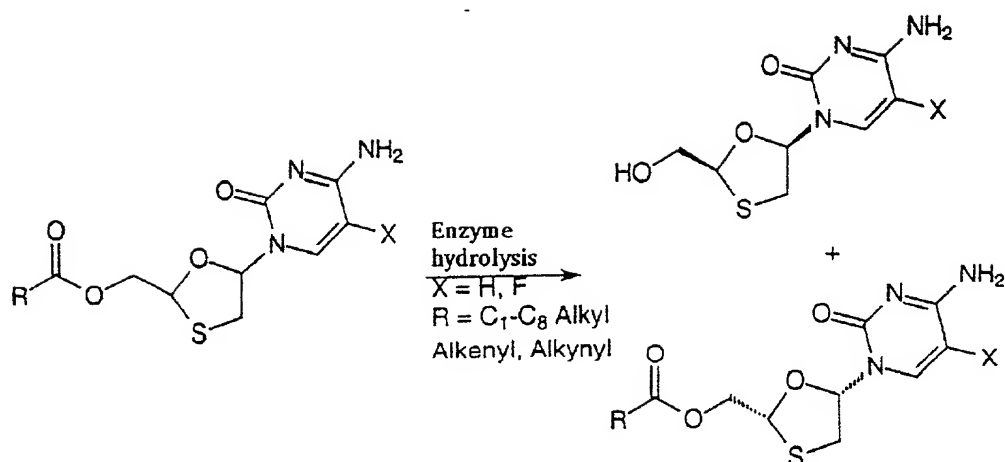
enzymatic racemate resolution is possible at the oxathiolanone stage. This is described by Liotta et al. (WO 91/11186). In this case, the stereoselection is achieved by enzymatic cleavage of an ester substituent in position 2 of the oxathiolane ring (equation 3).



Equation 3

An example which is mentioned is the hydrolysis of the butyric ester ($R = C_3H_7$) in the presence of pig liver esterase (PLE).

The second possibility is racemate resolution at the considerably more costly nucleoside stage. This process is described by Liotta et al. (*J. Org. Chem.* 1992, 57(21), pp. 5563-5565 and WO 92/14743). In this case, various ester acyl groups of the nucleoside racemate are stereoselectively eliminated in the presence of lipases or proteases (equation 4).



Equation 4

In some cases, high enantiomeric excesses ($ee(\text{ester}) > 98\%$) are achieved with good yields ($y(\text{ester}) \sim 45\%$).

An improvement of the process of WO 92/14743 is to be found in WO 00/22157 (inventors: Yao, Y. et al.) through the use of non-homogeneous reaction systems (addition of water-immiscible cosolvents) for resolution of racemates of oxathiolanyl-nucleosides.

These processes of racemate resolution at a very late stage entail the serious disadvantage of unnecessary use of materials and long plant usage, because the maximum yield of a racemate resolution is 50%. The remaining 50% (the compound with the wrong handedness) is usually discarded.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a process for preparing enantiopure 1,3-dioxolan-4-one and 1,3-oxathiolan-5-one derivatives which is cost-effective and avoids the disadvantages mentioned.

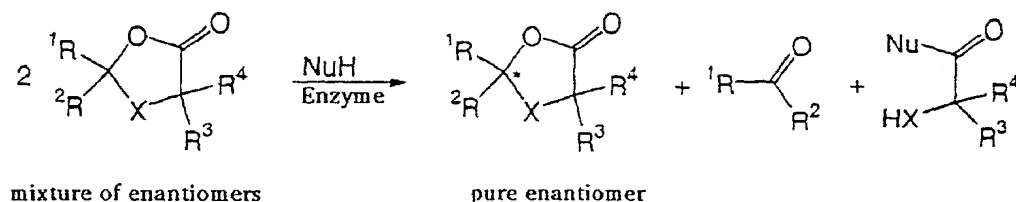
The object is achieved by a process in which a mixture containing enantiomeric 1,3-dioxolan-4-one or 1,3-oxathiolan-5-one derivatives and an enzyme with hydrolytic activity are brought into contact in the presence of a nucleophile, whereupon the dioxolanone or oxathiolanone ring of one enantiomer is cleaved by the enzyme with hydrolytic activity and, after the cleavage of one enantiomer has taken place, the uncleaved enantiomer of the 1,3-dioxolan-4-one or 1,3-oxathiolan-5-one derivative is isolated.

The process of the invention separates a mixture of enantiomers at the dioxolanone or oxathiolanone stage and thus provides an enantiopure derivative which then makes it possible for an enantiopure 1,3-dioxolanyl- or 1,3-oxathiolanyl-nucleoside to be prepared in a manner known per se.

1,3-Dioxolan-4-ones and 1,3-oxathiolan-5-ones have in the ring a hydrolysis-labile ester linkage which can be cleaved by an enzyme-catalyzed reaction. It has been found, surprisingly, that this ester linkage in the dioxolanone or oxathiolanone ring can be cleaved by an enzyme with hydrolytic activity both with high enantioselectivity and with high regioselectivity in relation to other hydrolysis-labile groups present in the compound.

The process of the invention therefore preferably comprises bringing a mixture containing enantiomeric 1,3-dioxolan-4-one or 1,3-oxathiolan-5-one derivatives into contact with an enzyme which is able to cleave an ester linkage in the presence of a nucleophile of the general formula NuH so that one enantiomer is preferentially cleaved.

This cleavage is depicted diagrammatically in equation 5.



Equation 5

where X = oxygen or sulfur and

the radicals R^1 and R^2 are different and are selected independently of one another from the group consisting of H, substituted or unsubstituted C_6-C_{18} -aryl, C_3-C_{18} -heteroaryl, C_1-C_{18} -alkyl, C_2-C_{18} -alkenyl, C_2-C_{18} -alkynyl, C_6-C_{18} -aryl- C_1-C_{18} -alkyl, C_3-C_{18} -heteroaryl- C_1-C_{18} -alkyl, C_6-C_{18} -aryl- C_2-C_{18} -alkenyl, C_3-C_{18} -heteroaryl- C_2-C_{18} -alkenyl, C_1-C_{18} -alkoxy- C_1-C_{18} -alkyl, C_1-C_{18} -alkoxy- C_2-C_{18} -alkenyl, C_6-C_{18} -aryloxy- C_1-C_{18} -alkyl, C_6-C_{18} -aryloxy- C_2-C_{18} -alkenyl, C_3-C_8 -cycloalkyl, C_3-C_8 -cycloalkyl- C_1-C_{18} -alkyl, C_3-C_8 -cycloalkyl- C_2-C_{18} -alkenyl, and $CR^8R^9-O_1-(CO)_m-R^{10}$ and the radicals R^3 and R^4 are selected independently of one another from the group consisting of substituted or unsubstituted C_1-C_{18} -aryl, C_1-C_{18} -heteroaryl, C_1-C_{18} -alkyl, C_2-C_{18} -alkenyl, C_2-C_{18} -alkynyl, C_6-C_{18} -aryl- C_1-C_{18} -alkyl, C_3-C_{18} -heteroaryl- C_1-C_{18} -alkyl, C_6-C_{18} -aryl- C_2-C_{18} -alkenyl, C_3-C_{18} -heteroaryl- C_2-C_{18} -alkenyl, C_1-C_{18} -alkoxy- C_1-C_{18} -alkyl, C_1-C_{18} -alkoxy- C_2-C_{18} -alkenyl, C_6-C_{18} -aryloxy- C_1-C_{18} -alkyl, C_6-C_{18} -aryloxy- C_2-C_{18} -alkenyl, C_3-C_8 -cycloalkyl, C_3-C_8 -cycloalkyl- C_1-C_{18} -alkyl, and C_3-C_8 -cycloalkyl- C_2-C_{18} -alkenyl or the radicals R^3 and R^4 form, together with the carbon to which they are bonded, an unsubstituted or substituted or a heteroatom-containing cycloalkylidene and Nu is OR^5 , SR^5 or

NR⁶R⁷, where

the radicals R⁵ are selected from the group consisting of H, substituted or unsubstituted C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl, C₂-C₁₈-alkynyl, C₆-C₁₈-aryl-C₁-C₁₈-alkyl, C₃-C₁₈-heteroaryl-C₁-C₁₈-alkyl, C₆-C₁₈-aryl-C₂-C₁₈-alkenyl, and C₃-C₁₈-heteroaryl-C₂-C₁₈-alkenyl, and the radicals R⁶ and R⁷ are selected

independently of one another from the group consisting of H, substituted or unsubstituted C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl, C₂-C₁₈-alkynyl, C₆-C₁₈-aryl, C₃-C₁₈-heteroaryl, C₆-C₁₈-aryl-C₁-C₁₈-alkyl, C₃-C₁₈-heteroaryl-C₁-C₁₈-alkyl, C₆-C₁₈-aryl-C₂-C₁₈-alkenyl, and C₃-C₁₈-heteroaryl-C₂-C₁₈-alkenyl

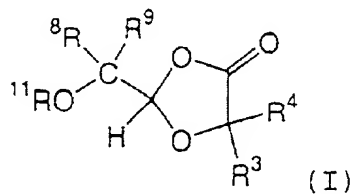
and the radicals R⁸ and R⁹ are selected independently of one another from the group consisting of substituted or unsubstituted C₆-C₁₈-aryl, C₃-C₁₈-heteroaryl, C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl, C₂-C₁₈-alkynyl, C₆-C₁₈-aryl-C₁-C₁₈-alkyl, C₃-C₁₈-heteroaryl-C₁-C₁₈-alkyl, C₆-C₁₈-aryl-C₂-C₁₈-alkenyl, C₃-C₁₈-heteroaryl-C₂-C₁₈-alkenyl, C₁-C₁₈-alkoxy-C₁-C₁₈-alkyl, C₁-C₁₈-alkoxy-C₂-C₁₈-alkenyl, C₆-C₁₈-aryloxy-C₁-C₁₈-alkyl, C₆-C₁₈-aryloxy-C₂-C₁₈-alkenyl, C₄-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₁₈-alkyl, and C₄-C₈-cycloalkyl-C₂-C₁₈-alkenyl or the radicals R⁸ and R⁹ form, together with the carbon to which they are bonded, an unsubstituted or substituted or a heteroatom-containing cycloalkylidene, and m and n are, independently of one another, 0 or 1, and the following applies to the radical

R^{10} : if m is 0 then the radical R^{10} is selected from the group consisting of substituted or unsubstituted C_1 - C_{18} -alkyl, C_2 - C_{18} -alkenyl or C_2 - C_{18} -alkynyl, substituted or unsubstituted C_6 - C_{18} -aryl, C_3 - C_{18} -heteroaryl, and substituted or unsubstituted silaalkyl or silaaryl, and if m is 1 then the radical R^{10} is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted C_1 - C_{18} -alkyl, C_2 - C_{18} -alkenyl or C_2 - C_{18} -alkynyl.

Where the radicals are substituted radicals, these are preferably substituted by alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxyl, alkoxy, carboxylate, alkoxycarbonyl, amino, nitro or halo radicals.

Where the abovementioned radicals contain a heteroatom, it is preferably O, N or S.

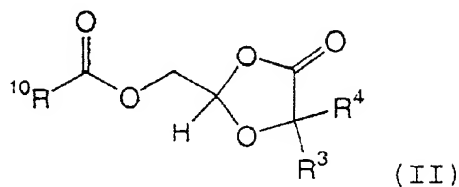
Mixtures of enantiomers of the general formula (I)



where R^3 , R^4 , R^8 and R^9 have the meaning mentioned above, and R^{11} are substituted or unsubstituted, branched or unbranched C_1 -

C₁₈-alkyl, C₂-C₁₈-alkenyl or C₂-C₁₈-alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted silaalkyl or silaaryl, or R¹¹ is COR¹⁰ where R¹⁰ has the meaning mentioned above, are preferably used.

Mixtures of enantiomers of the general formula (II)



where R³ and R⁴ have the meaning mentioned above, and R¹⁰ is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl and C₂-C₁₈-alkynyl, are particularly preferably used.

The nucleophile NuH is preferably an oxygen-containing nucleophile OR⁵.

The oxygen-containing nucleophile is particularly preferably a lower, unbranched alcohol, (e.g. methanol (R⁵ = CH₃) or ethanol (R⁵ = CH₂CH₃)) or water (R⁵ = H).

All enzymes able to cleave an ester linkage are in

principle suitable for the process of the invention.

Preference is given to a lipase or esterase of class 3.1 of the international enzyme nomenclature, Committee of the International Union of Biochemistry and Molecular Biology. Because they are easy to obtain, particular preference is given to lipases or esterases of microbial origin, pig pancreatic lipase, horse liver esterase or pig liver esterase.

Examples of enzymes of microbial origin which may be mentioned are enzymes from fungi, yeasts or bacteria such as, for example, *Alcaligenes* sp., *Aspergillus niger*, *Aspergillus oryzae*, *Bacillus* sp., *Bacillus stearothermophilus*, *Bacillus thermoglucosidasius*, *Candida antarctica*, *Candida lipolytica*, *Candida rugosa*, *Chromobacterium viscosum*, *Geotrichum candidum*, *Mucor miehei*, *Penicillium camembertii*, *Penicillium roquefortii*, *Pseudomonas cepacia*, *Pseudomonas fluorescens*, *Pseudomonas* sp., *Rhizomucor javanicus*, *Rhizopus arrhizus*, *Rhizopus niveus*, *Saccharomyces cerevisiae*, *Thermoanaerobium brockii*, *Thermomyces lanuginosa*. Particular preference is moreover given to lipases and esterases from *Candida* species such as, for example, *Candida antarctica* B.

Very particular preference is given to Novozym® 435,

525 (commercially available from Novo, Denmark), Chirazym® L2, E1, E2 and L7 (commercially available from Boehringer Mannheim, Germany) as enzyme.

The enzyme is employed in the reaction directly or in immobilized form bound to a wide variety of carriers.

An immobilized form can be prepared in a manner known per se. This is possible, for example, by the enzyme being dissolved in a buffer at a suitable pH and then being passively adsorbed onto the carrier such as, for example, diatomaceous earth (Celite®), activated carbon, alumina, silica gel, kieselguhr, monodisperse soluble organosiloxane particles or resins (e.g. Amberlite®, Dowex®). An alternative possibility is for the enzymes also to be covalently bonded to the carrier (e.g. polystyrene or epoxy resins such as Eupergit®). An enzyme which has been bound to a carrier in this way, for example, can be dried by lyophilization.

The amount of enzyme to be employed in the process of the invention depends on the nature of the precursor and of the product and on the activity of the enzyme preparation. The amount of enzyme which is optimal for the reaction can be established by simple preliminary tests.

Depending on the enzyme, the enzyme/substrate ratio, calculated as molar ratio between enzyme and dioxolanone/oxathiolanone derivative, is usually between 1:1 000 and 1:50 000 000 or more, preferably from 1:10 000 to 1:5 000 000.

The process of the invention can be carried out both in pure nucleophile (NuH) as solvent and in mixtures of the nucleophile (NuH) with aprotic or protogenic solvents or mixtures of solvents as long as these do not affect the reactivity of the enzyme with hydrolytic activity or lead to unwanted side reactions.

The reaction is advantageously carried out in a mixture of the nucleophile and a suitable solvent. Examples of suitable solvents are aliphatic or aromatic hydrocarbons such as hexane, cyclohexane, petroleum ether or toluene, halogenated hydrocarbons such as methylene chloride or chloroform, ethers such as methyl tert-butyl ether (MTBE), diethyl ether, diisopropyl ether, THF or dioxane, esters, acetonitrile or, where appropriate, alcohols which do not represent a nucleophile in relation to the abovementioned enzymatic reaction, such as, for example, tertiary alcohols, or mixtures of said compounds.

The nucleophile/solvent ratio (v/v) is in this case preferably in a range from 1:10 000 to 1 000:1.

Mixtures of the nucleophile with aprotic solvents such as MTBE or diisopropyl ether in a nucleophile/solvent ratio (v/v) of from 1:100 to 100:1 are particularly preferred.

If water is used as nucleophile ($\text{Nu} = \text{OH}$), it is possible for maintenance of a preset pH to adjust the latter by adding a buffer. An $\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4$ buffer with a pH of 7.0 is preferably used for this purpose. It is also possible for the same purpose to meter in an aqueous alkali, preferably a solution of an alkali metal hydroxide in water, particularly preferably an aqueous solution of NaOH or KOH.

The reaction is advantageously carried out at a temperature between 0°C and 75°C , preferably between 10°C and 60°C , particularly preferably between 20°C and 50°C .

The reaction times depend on the substitution pattern of the dioxolanone, choice of the nucleophile and solvent and the nature and amount of the enzyme and are between 10 minutes and 7 days. The reaction times are preferably between

1 and 48 hours.

The progress of the reaction can easily be followed by conventional methods, for example by HPLC. The progress of the reaction can preferably be determined by measuring the change in the optical rotation of the reaction solution in a polarimeter. The progress of the reaction is particularly preferably determined on line by measuring the optical rotation in a subsidiary circuit of the reactor. The termination of the reaction can depend on the desired result (high conversion, high enantiomeric excess of the substrate). In the ideal case, the reaction is terminated when the conversion is 50% with a high enantiopurity in the substrate.

The reaction is preferably terminated for example by separating the substrate or the product from the enzyme, for example by extraction of the aqueous phase or filtration. The reaction can also be stopped by inactivating the enzyme, for example by thermal or chemical denaturation.

If the reaction is carried out by repeated, continuous pumping of the reaction solution through a container packed with enzyme (a particularly preferred procedure), the reaction is preferably terminated by

terminating the pumping.

The uncleaved, pure enantiomer is preferably isolated by removing the byproducts of the reaction and the solvent.

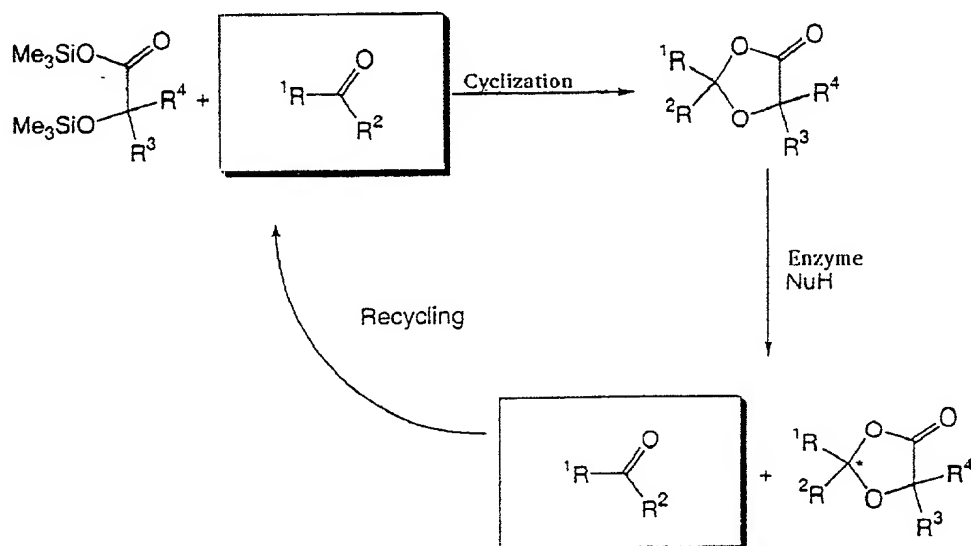
The free carbonyl compound R^1COR^2 resulting from the cleavage of a 1,3-dioxolan-4-one or 1,3-oxathiolan-5-one ring and the acid derivative $HXCR^3R^4CONu$ can be removed from the reaction solution by simple physical operations. This preferably takes place by distillation.

It is additionally possible for further breakdown products formed on cleavage of other functional groups in the molecule to be removed easily. This preferably takes place by distillation.

It is preferred for the low-boiling compounds to be removed first by distillation. It has been found, surprisingly, that the alcohol ($R^1 = H$, $R^2 = CH_2OH$) which is a byproduct of the racemate resolution of an ester dioxolanone ($X = O$; $R^1 = H$, $R^2 = CH_2-O-(CO)-R^{10}$) can be removed by simple extraction, preferably with water.

The carbonyl compound resulting from the enzymatic

reaction is an important, costly precursor for the synthesis of racemic 1,3-dioxolan-4-one and 1,3-oxathiolan-5-one compounds. It is preferably employed, in order to save chemicals and costs, in the synthesis of 1,3-dioxolan-4-ones and 1,3-oxathiolan-5-ones (see scheme 1).



Scheme 1: Recycling of the carbonyl compound resulting from the racemate resolution for the example of 1,3-dioxolan-4-ones

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Other objects and features of the present invention will become apparent from the following detailed description

considered in connection with the accompanying examples. It is to be understood, however, that the examples are designed as an illustration only and not as a definition of the limits of the invention.

Example 1: (4-oxo-1,3-dioxolan-2-yl)methyl (+)-(R)-2-methylpropanoate (batch process)

50.0 g (0.27 mol) of racemic (4-oxo-1,3-dioxolan-2-yl)methyl 2-methylpropanoate ($X = O$; $R^1 = H$; $R^2 = CH_2-O-(CO)-CH(CH_3)_2$; $R^3, R^4 = H$) are dissolved in a mixture of 185 ml of MTBE and 185 ml of methanol ($Nu = OCH_3$) in a 1 l 4-necked flask. 2.6 g of Novozym® 435 are added to this solution, and the mixture is stirred vigorously.

A polarimeter is connected via a bypass system to the 4-necked flask and is used to follow the progress of the reaction through measurement of the optical rotation of the solution. When the desired enantiopurity (reaction followed by chiral GC) is reached, the reaction is terminated by filtering the reaction mixture to remove undissolved enzymes. The reaction mixture is then concentrated in vacuo. The residue is then taken up in 100 ml of MTBE and washed twice

with 100 ml of water each time. The organic phase is dried over Na_2SO_4 and then freed of solvent in vacuo. The crude product is purified by distillation.

Yield: 10.3 g (0.05 mol; 20%)

Boiling point: 55°C (0.02 mbar)

$[\alpha]_D^{20} = +19.8$ (neat); ee > 98%


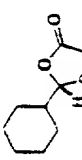
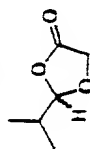
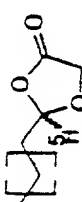
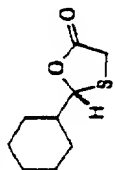
Example 2: (4-Oxo-1,3-dioxolan-2-yl)methyl (+)-(R)-2-methylpropanoate (column process)

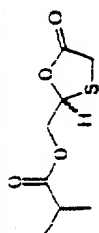
50.0 g (0.27 mol) of racemic (4-oxo-1,3-dioxolan-2-yl)methyl 2-methylpropanoate ($X = \text{O}$; $R^1 = \text{H}$; $R^2 = \text{CH}_2\text{-O-(CO)-CH(CH}_3\text{)}$; $R^3, R^4 = \text{H}$) are dissolved in a mixture of 185ml of MTBE and 185 ml of methanol ($\text{Nu} = \text{OCH}_3$) in a thermostatted 0.6 l glass flask. A separate glass column is packed with 1.3 g of Novozym® 435, and the substrate/solvent mixture is pumped via a tubing system through the glass column (flow rate 600 ml/h).

The reaction is stopped (after ~ 25 h) by terminating the pumping, and the crude product is purified as described in example 1.

Examples 3-8:

The following examples were carried out in accordance with the method of example 1.

	Substituents in equation 5	Racemate	Product	Selectivity according to σ_{H}
3	$X = O; R^1 = H; R^2 = -CH_2-C_6H_5$ $R^3, R^4 = H$		(+)-2-Methylphenyl-1,3-dioxolan-4-one	11
4	$X = O; R^1 = H; R^2 = -C_6H_{11}$ $R^3, R^4 = H$		(+)-2-Cyclohexyl-1,3-dioxolan-4-one	65
5	$X = O; R^1 = H; R^2 = -CH(CH_3)_2$ $R^3, R^4 = H$		(+)-2-iso-Propyl-1,3-dioxolan-4-one	14
6	$X = O; R^1 = H; R^2 = -C_7H_{15}$ $R^3, R^4 = H$		(+)-2-Heptyl-1,3-dioxolan-4-one	13
7	$X = S; R^1 = H; R^2 = -C_6H_{11}$ $R^3, R^4 = H$		(+)-2-Cyclohexyl-1,3-oxathiolan-5-one	65

8	$X = S, R^1 = H; R^2 = -CH_2O(CO) -$ $CH(CH_3)_2$ $R^3, R^4 = H$		(+) - Isobutyryloxy- methyl-1,3-oxathiolan- 5-one	65
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* Chen, C.-S. et al., J. Am. Chem. Soc. 104, 7294-7299 (1982)

Accordingly, while only several embodiments of the present invention have been shown and described, it is obvious that many changes and modifications may be made thereunto without departing from the spirit and scope of the invention.